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Risk Factors for Preeclampsia in Pregnant Women with Pregestational Diabetes

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ABSTRACT

Purpose: *To estimate the incidence of preeclampsia in pregnant women with pregestational diabetes and to identify risk factors for preeclampsia.*

Material and methods: *A retrospective cohort study of pregnant women with pregestational diabetes was conducted and compared with a random sample of non-diabetic pregnant women from the population served in the period from January 2017 to August 2019 at the Obstetrics Service of the Women's Hospital. By means of multiple logistic regression the risk factors for preeclampsia were estimated.*

Results: *10% and 90% of the cases were type 1 and type 2 diabetes mellitus respectively. The incidence of preeclampsia in pregestational diabetes mellitus was 22.5%. Chronic hypertension (OR: 28, CI95%4.8,164) for global PE, nulliparity (OR:6.8, CI95%1.6,36.2) for PE with SF, metabolic disorder (OR:8.4, CI95%1.3,54) for early-onset PE.*

Conclusions: *Chronic hypertension, nulliparity, and metabolic disorder were risk factors for preeclampsia in pregnant women with pregestational diabetes.*

Keywords

Pregestational diabetes, Type 1 diabetes mellitus, type 2 diabetes mellitus, Preeclampsia, Pregnancy.

Introduction

Pregestational diabetes mellitus (PGDM) refers to women diagnosed with type 1 diabetes mellitus (DM1) or type 2 diabetes mellitus (DM2) prior to pregnancy or diagnosed during the first trimester of pregnancy. The prevalence of all forms of diabetes in pregnancy is reported worldwide between 5 and 20% and in Mexico the prevalence fluctuates between 3 and 19.6% [1].

In the global population it is estimated that approximately 6-7% of pregnancies are complicated by diabetes; 88-90% are women with gestational diabetes, and 10-12% are pre-pregnancy (DM1: 35% and DM2: 65%) [2]. Strict metabolic control prevents congenital central nervous system, cardiovascular, renal and skeletal muscle malformations and lowers the high incidence of miscarriages

[1,3]. Preeclampsia (PE), as a serious and frequent disease, affects about 3-8% of all pregnancies and increases the risk of morbidity in the mother; Several risk factors for the development of pre-eclampsia have been found in studies carried out in Mexico [4,5], however none of them investigate the risk factors for PE in PGDM.

In Canada, they found that diabetes mellitus was a risk factor for both early and late-onset PE [6,7]. It has also been shown that the risk of PE increases 2 to 4 times in women who experience DM1 or DM2 [7,8]. Maternal morbidity varies according to the type of pre-eclampsia, with the early and severe forms being the most dangerous [6,9,10].

In our hospital unit, the possible relationship between PE and PGDM is unknown. The prevalence of obesity in pregnancy in our environment has reached 40%, and we know the relationship that this has with both PGDM and PE, so it would be relevant to determine the incidence of pre-eclampsia and the risk factors for it in patients with pregestational diabetes mellitus

Material and Methods

A nested case-control study was conducted in a retrospective cohort of pregnant women with PGDM compared with a random sample of non-diabetic pregnant women served in the period January 2017 to August 2019 at the Obstetrics Service of the Women's Hospital. The diagnosis of PGDM was based on the pre-pregnancy diagnosis of type 1 or type 2 diabetes mellitus and that they were receiving medical treatment and in both cases were initially attended by first level doctors in Urban Health Centers of Units of municipalities in Northwest Mexico. In neither case was the diagnosis of diabetes mellitus (DM) made during pregnancy.

Maternal and perinatal characteristics were obtained through the analysis of the electronic file, excluding those pregnant women diagnosed with liver diseases, autoimmune diseases, immune thrombocytopenic purpura (ITP), gestational diabetes and those with unreliable laboratory tests or incomplete files. Sociodemographic variables, maternal and perinatal characteristics, preeclampsia characteristics and its phenotypic forms were analyzed.

Since this is a comparative and retrospective observational study in records, there is no risk based on the review of records of pregnant women attended at the Women's Hospital (Hospital de la Mujer) in Northwestern Mexico, who previously authorized and signed informed consent which was previously submitted for evaluation and authorization by the Ethics Committee of the Women's Hospital.

Statistical analysis

From an Excel database of 130 pregnant women consisting of 40 patients with PGDM treated in the study period and 90 healthy patients from the study period (randomly extracted with the Excel program) treating a selection of 2 controls for each case. For the descriptive and inferential analysis of the quantitative variables, means, medians, interquartile range (ICR) and standard deviation (SD) were obtained, and for categorical variables, frequencies and percentages were obtained. The comparison of means/medians for quantitative variables used the analysis of variance or the Kruskal-Wallis test if the variable had normal distribution or not respectively. The association between qualitative variables was tested using Pearson's chi-square test. To identify risk factors, the odds ratio (OR) was estimated using multiple logistic regression. A p-value lower than 0.05 was considered statistically significant. The data were analyzed using the Stata 14.

Results

From January 2017 to August 2019 there were 17,144 births with an overall prevalence of diabetes of 235 (1.37%). The incidence of gestational diabetes mellitus (GDM) was 1.14% (n=195) and 40 (0.23%) were PGDM. DM1 was 4 (10%) and DM2 was 36 (90%) cases.

The median age of participants was 30.5 (ICR=7.5) and 22.5 (ICR=9) years for PGDM and healthy controls, respectively, p=0.0001. Gestational age was 37 (ICR=1) and 39 (ICR=2) for PGDM and healthy controls respectively, p=0.0001. BMI was 33.2 (ICR=7.3) and 27.4 (ICR=5.7) kg/m^2 for PGDM and healthy controls respectively, p=0.0001. The weight of the newborn was 3.500 (ICR=795) and 3.275 (ICR=660) grams for PGDM and healthy controls respectively. p=0.059.

Table 1: Maternal characteristics and perinatal outcomes in participating pregnant women.

	DM1 (n=4)	DM2 (n=36)	Healthy (n=90)
	n (%)	n (%)	n (%)
Advanced maternal age (age>35)	0 (0.0)	12 (33.3)	4 (4.4)
Nullipara	1 (25.0)	8 (22.2)	37 (41.11)
Multipara	0 (0.0)	14 (38.9)	21 (23.3)
Grand multipara	0 (0.0)	6 (16.7)	5 (5.6)
Obesity	2 (50.0)	26 (72.2)	30 (33.3)
Chronic high blood pressure	1 (25.0)	6 (16.7)	0 (0.0)
Metabolic disorders	4 (100.0)	18 (50.0)	0 (0.0)
Pre-eclampsia	1 (25.0)	0 (0.0)	1 (1.1)
Total Preeclampsia	1 (25.0)	8 (22.2)	6 (6.7)
Severe preeclampsia	1 (25.0)	2 (5.6)	5 (5.6)
Non-severe preeclampsia	0 (0.0)	6 (16.7)	1 (1.1)
Early Preeclampsia	1 (25.0)	3 (8.3)	1 (1.1)
Late preeclampsia	0 (0.0)	5 (13.9)	5 (5.6)
Cesarean section	4 (100.0)	29 (80.6)	40 (44.4)
Oligohydramnios	0 (0.0)	3 (8.3)	2 (2.2)
Polyhydramnios	2 (50.0)	6 (16.7)	0 (0.0)
Prematurity	2 (50.0)	7 (19.4)	9 (10.0)
Low birth weight	1 (25.0)	4 (11.1)	8 (8.9)
IUGR	0 (0.0)	1 (2.8)	1 (1.1)
Stillborn	0 (0.0)	1 (2.8)	0 (0.0)

DM1: Type 1 diabetes mellitus; DM2: Type 2 diabetes mellitus; IUGR: Intrauterine growth restriction.

Age over 35 years, obesity, preeclampsia, prematurity and polyhydramnios were the main characteristics of pregnant women with DM1 and DM2 compared to healthy women. Table

1. Manifestations in PE with severe features (SF) were systolic blood pressure (SBT) greater than or equal to 160 mmHg and/or diastolic blood pressure (DBT) greater than or equal to >110 mmHg in 75%; persistent or de novo headache, visual or cerebral alterations in 75% of cases; increase in AST or ALT >70 in 25%; epigastric pain or pain in right hypochondrium and elevation of serum creatinine >1.1 in 12.5%. Median age of preeclamptic diabetic women was 31 (ICR=3) years, BMI was 34.4 (ICR=12.1) kg/m^2, average gestational age was 37 (ICR=4) weeks and newborn weight was 3,200 (ICR=830) grams; chronic hypertension, obesity and nulliparity were the main characteristics of diabetic patients with preeclampsia (Table 2).

Table 2: Maternal, obstetric and perinatal characteristics of preeclamptic

Variables	n (%)
Over 35 years old	2 (22.2)
Chronic high blood pressure	**5 (55.5)**
Overweight	2 (22.2)
Obesity	**7 (77.7)**
Nullipara	**5 (55.5)**
Multipara	2 (22.2)
Polyhydramnios	2 (22.2)
Cesarean section	8 (88.8)
Fetal Macrosomia	3 (33.3)
Low birth weight	2 (22.2)
Prematurity	4 (44.4)
Stillborn	1 (6.7)

The frequency of PE was 6.7, 22.5 and 71.4% in healthy controls, pregestational diabetics with chronic hypertension and PGDM respectively. The frequency of PE was 6.7, 22.5 and 71.4% in healthy controls, PGDM and pre-pregnancy diabetic women with chronic hypertension, respectively. The history of SAH was an independent risk factor for PE in general, adjusted for age over 35, obesity and nulliparity; likewise, it was for early, late and non-severe PE. The independent risk factor for PE with SF was nulliparity. Metabolic disorder was a risk factor for early-onset PE Table 3.

Discussion

In a study conducted in China from January to June 2016 the cumulative prevalence of PGDM was 0.472% of which 30.3% were diagnosed before pregnancy and 69.7% after conception; in the same study, maternal age, BMI and incidence of macrosomia were higher in patients with PGDM but gestational age was lower, similar results to ours [11]. In Denmark, they found a cumulative incidence of PGDM of 0.36% over the period 1978 to 2011 and found that there was an elevated risk of heart disease which did not vary over time or with the subtype of diabetes [12]. Another study conducted in indigenous groups in Canada from 1996 to 2010 found a 1.3% incidence of PGDM in those known to have a higher genetic predisposition for diabetes [13]. In the United States, the prevalence of PGDM is known to be 1-2% of all pregnancies and its frequency continues to increase [14,15]. Placentation in both diabetic and hypertensive patients occurs abnormally and consequently leads to poor placental perfusion and subsequent oxidative stress which represents one of the most important physio-pathological mechanisms for developing PE [16,17].

In Germany, they found no association between PGDM and preeclampsia, however, they mention as we do that maternal obesity is more common in pregnant women with PGDM [18]. It is known that African-American race, chronic hypertension is more associated to early-onset PE and that advanced maternal age to late-onset PE, situation that we could only confirm in the first case [6]. In Brazil, in a cohort study of women with PGDM conducted from 2005 to 2015, they obtained a 30% prevalence of PE and demonstrated that DM1, chronic hypertension and systolic blood pressure ≥ 124 mmHg as well as excessive gestational weight gain were independent riskfactors for PE [19-21].

The prevalence of pregnant women over 35 years of age increased from 6.2% in 1980 to 22.3% in 2016 and the factors that favor PE are inadequate prenatal control, hypertension, type 2 diabetes

Table 3: Risk factors for preeclampsia in pregnant women with pregestational diabetes.

Risk Factors	**Total EP OR (IC95%)**		**Early PE OR (IC95%)**		**Late PE OR (IC95%)**		**Severe PE OR (IC95%)**		**Non-Severe PE OR (IC95%)**	
	NA	A	NA	A	NA	A	NA	A	NA	A
SAH	**28.3** (4.8-164)	‡**22.7** (3.7-138.6)	**16.0** (2.2.118.3)	***8.5** (1.0-75.2)	**12.4** (2.3-66.7)	‡**9.31** (1.6-53.33), ***16.9** (2.4,118.6)	2.8 (0.3-26.2)	--	**53.3** (8.1-351.3)	***46.7** (6.1-360.5)
Obesity	2.8 (0.9-8.7)	--	1.9 (0.3-11.8)		3.2 (0.8-1.8)	--	2.2 (0.5-9.5)	--	3.3 (0.6-1.7)	--
Age Over 35 years old	2.0 (0.5-7.9)	--	1.8 (0.2-17.5)		1.9 (0.4-9.8)	--	2.6 (0.5-13.9)	--	1.2 (0.13-10.6)	--
Nullipara	2.3 (0.8-6.9)	--	7.9 (0.9-73)		1.2 (0.3-4.6)	--	**6.2** (1.2-31.8)	***6.8** (1.3-36.2), †**6.06** (1.16,31.5)	0.7 (0.1-3.9)	--
Metabolic Disorder	2.9 (0.9-9.5)	--	**8.4** (1.3-54.0)	†5.13 (0.68-38.5)	1.3 (0.2-6.3)	--	1.7 (0.3-9.0)	--	4.1 (0.8-19.8)	--

SAH: Systemic arterial hypertension; **NA:** not adjusted; **A:** adjusted **†:** adjusted for SAH; **‡:** adjusted for obesity; ***:** adjusted for metabolic disorders.

mellitus, obesity, smoking during pregnancy and previous preeclampsia, a situation that we could not confirm in our work [6,22,21]. The mechanisms that favor the development of PE in nulliparous women are high levels of soluble tyrosine kinase 1 similar to fms (sFlt-1) as well as the relation of sFlt1/PlGF (placental growth factor) that favor an antiangiogenic state and consequently the development of preeclampsia, which we observed in this study where nulliparity was an independent risk factor for PE with severe features [21,23,24].

The history of previous PE in patients with PGDM is a risk factor for PE, a situation that we could not demonstrate in our population [5,21]. In the present study, metabolic distress, the history of chronic hypertension, favors early-onset PE but not PE with severe features. Interestingly, early and severe forms of PE were more frequent in type 1 diabetics where the lack of insulin production causes metabolic distress. The analysis of syncytiotrophoblast gene ontology, the deregulation of immune functions, morphogenesis, transport, responses to vascular endothelial factor (VEGF) and progesterone can be aggravated by metabolic disorder and particularly in PE with SF [25]. Late-onset PE and non-severe PE were more frequent in DM2, where metabolic disturbance was less frequent and insulin resistance predominated and oxidative stress was less severe than in DM1, which allowed expressions of PE without severity data or the late form. Metabolic disruption, oxidative stress and systemic inflammation influence the development of all forms of PE. Metabolic disorder impacts differently in pregestational diabetes, these results corroborate that adequate glucose control prevents maternal and fetal complications [20].

The strength was to have demonstrated in Mexican pregnant women the phenotypes of preeclampsia and their risk factors in pregnant women with PGDM. Likewise, that early and severe forms of PE occur mainly in DM1 and that late and non-severe PE are more frequent in DM2 which makes us hypothesize that failures in insulin signaling at a post-receptor level have an important influence at a molecular level in the development of preeclampsia in this particular group of patients. The weakness was the very low frequency of DM1 and DM2 to make definitive conclusions, and research on preeclampsia in PGDM with larger samples should be done.

Conclusion

The incidence of preeclampsia in pregestational diabetes mellitus was 22.5%. Systemic arterial hypertension, nulliparity, and metabolic disorder were risk factors for PE in diabetic pregnant women. Early-onset and PE with SF phenotypes are more common in DM 1 and non-severe and late-onset PE phenotypes were more common in DM 2.

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